Willers, S. M., Jonker, M. F., Klok, L., Keuken, M. P., Odink, J., van den Elshout, S., Sabel, C. E., Mackenbach, J. P., & Burdorf, A. (2016). High resolution exposure modelling of heat and air pollution and the impact on mortality. *Environment International*, *89-90*, 102-109. https://doi.org/10.1016/j.envint.2016.01.013

Peer reviewed version

Link to published version (if available):
10.1016/j.envint.2016.01.013

Link to publication record in Explore Bristol Research
PDF-document

This is the author accepted manuscript (AAM). The final published version (version of record) is available online via Elsevier at http://www.sciencedirect.com/science/article/pii/S0160412016300137.

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Original Article

Willers S M, Marcel Jonker, Lisette Klok, Menno P. Keuken, Jennie Odink, Sef van den Elshout, **Sabel C E,** Johan P. Mackenbach, Alex Burdorf (2016) High resolution exposure modelling of heat and air pollution and the impact on mortality, Environment International, 89-90, 102-109.

High resolution exposure modelling of heat and air pollution and the impact on mortality

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Running title

Heat, air pollution and mortality

Abstract (201 words)

Background: Elevated temperature and air pollution have been associated with increased mortality. Exposure to heat and air pollution, as well as the density of vulnerable groups varies within cities. The objective was to investigate the extent of neighbourhood differences in mortality risk due to heat and air pollution in a city with a temperate maritime climate.

Methods: A case-crossover design was used to study associations between heat, air pollution and mortality. Different thermal indicators and air pollutants (PM_{10}, NO_2, O_3) were reconstructed at high spatial resolution to improve exposure classification. Daily exposures were linked to individual mortality cases over a 15 year period.

Results: Significant interaction between maximum air temperature (Ta_{max}) and PM_{10} was observed. During "summer smog" days (Ta_{max} > 25 ºC and PM_{10} > 50 µg/m^3), the mortality risk at lag 2 was 7% higher compared to the reference (Ta_{max} 15 °C and PM_{10} 15 µg/m^3). Persons above age 85 living alone were at highest risk.

Conclusion: We found significant synergistic effects of high temperatures and air pollution on mortality. Single living elderly were the most vulnerable group. Due to spatial differences in temperature and air pollution, mortality risks varied substantially between neighbourhoods, with a difference up to 7%.

Key words

heat stress, air pollution, mortality, case-crossover study, vulnerable groups, spatial variation

Conflicts of Interest

The authors declare they have no actual or potential competing financial interests.

Ethics Statement

Mortality data and individual (socio-economic) characteristics were available from the mortality database of Statistics Netherlands (CBS). This dataset is completely anonymous and the Dutch Code of Conduct for Medical Research allows the use of anonymous data for research purposes without an explicit informed consent (www.federa.org).

1. Introduction

Elevated temperatures are associated with increased mortality,[1-5] with air pollution acting as a confounder or effect modifier.[3,6,7] However, the threshold and severity of heat effects varies by country and latitude, which can be explained by differences in various physiological as well as behavioural factors.[5,8] Examples of these factors are acclimatisation to hot weather and the ability to thermoregulate the body, as well as time spent indoors, and the use of air conditioning.[4] These factors may also differ within a population, which makes certain subgroups more susceptible to heat effects than others.[1,3,9,10]

Regarding heat exposure it is known that urban areas typically have higher temperatures than suburban or surrounding areas, a phenomenon known as the Urban Heat Island (UHI) effect.[11] The UHI effect is influenced by urban characteristics such as building height, material and orientation as well as the amount of green space and water, which all vary between urban areas. Generally, the dry and dark urban surfaces will become hotter compared to lighter, moist or shaded surfaces because of easier absorption of sunlight. [12]

Besides differences in heat exposure, there are also differences in exposure to air pollution, and density of potentially vulnerable groups within a city. Hence, substantial differences in heat-mortality risks between urban neighbourhoods are expected.

The objective and novelty of this study was to investigate the extent of effect modification between heat and air pollution, and if spatial differences in exposure within a city lead to discernible differences in mortality risk between neighbourhoods. This was done using thermal, air pollution and mortality data on the city of Rotterdam, a Dutch city with a maritime temperate climate and a multi-ethnic and socioeconomic diverse population. We used a case-crossover design in combination with high resolution exposure modeling to calculate associations and to examine possible interactions between heat, air pollution and natural-cause mortality. We also investigated if certain subgroups, determined by sex, age, ethnicity, marital status and household income, were more susceptible to heat-related mortality than the urban population as a whole.

2. Material and methods

2.1. Study population

The associations between heat, air pollution and mortality were studied in Rotterdam over the period 1995-2009. Rotterdam is a city with around 600.000 inhabitants in the Netherlands, located in Northern Europe close to the North Sea, and therefore benefits from relatively cool and clean sea breezes. Rotterdam consists of 90 neighbourhoods with an average size of 2.3 km^2, and has a large port and industrial area.

The study population consisted of natural-cause mortality cases in Rotterdam during this period, which were retrieved from the mortality database of Statistics Netherlands (in Dutch: Centraal Bureau voor de Statistiek (CBS)). Natural-cause mortality cases were selected according to the International Classification of Disease (ICD) codes 9th (for the year 1995) and 10th revision (1996-2009), excluding death due to all external causes such as accidents, suicides, poisoning etc. Information about age, sex, marital status, ethnicity and household income (defined as a standardised measure for the prosperity of a household and corrected for differences in household size and composition)[13] of these cases were available from the same database. This database is protected by strict privacy regulations, so the analysed data were completely anonymous. The Dutch Code of Conduct for Medical Research allows the use of anonymous data for research purposes without an explicit informed consent.[14]

Daily, neighbourhood specific exposure data on heat and air pollution for the study period were merged to the mortality dataset, and matched by neighbourhood of residence and date of death of the cases in our study. Exposure was averaged on neighbourhood level because the exact home addresses of the mortality cases were not accessible due to privacy regulations.

2.2. Heat exposure assessment

Besides temperature, other meteorological factors such as humidity, wind speed and solar radiation, are also important in determining the outdoor thermal environment. Therefore, daily exposure to heat was assessed using three indices: daily maximum air temperature (Ta), mean radiant temperature (Tmrt),[15,16] and the Universal Thermal Comfort Index (UTCI).[16]

Tmrt is a parameter that influences the energy balance and thermal comfort (heat load) of humans, and therefore useful when assessing the impact of heat on people's health.[15] Tmrt is directly influenced by urban geometry and surface material, and therefore also a good measure to identify urban hot spots. Tmrt can be calculated from the total radiation flux density absorbed by the body, which is the sum of all short- and longwave radiation fluxes (both direct and reflected) to which a human body is exposed, the emissivity of the human body, and the Stefan-Boltzmann constant according to the Stefan-Boltzmann law formulas described in the paper of Thorsson et al.[15] Total radiation flux densities can be modelled using inputs of global shortwave radiation, air temperature and relative humidity.[16]

The UTCI is an indicator sensitive to changes in radiation, humidity and wind speed in both cold and warm conditions, and is often applied in public weather services, public health services, urban planning and design.[17]

Meteorological data were retrieved from the Royal Netherlands Meteorological Institute (KNMI) station at Rotterdam Airport, located north of Rotterdam (approximately 3 km distance from city centre). Air temperature, relative humidity, wind speed and global radiation were used as input for the models that constructed the various daily heat indices for the different neighbourhoods in Rotterdam during the study period.

Neighbourhood-specific daily air temperature was modelled according to the method of Klok et al.[17] The Urban Heat Island effect in the city centre of Rotterdam (UHI_city centre) was estimated as the annual mean difference in air temperature between a weather station in the city centre (near Central Station) and Rotterdam Airport. This was found to be 1.2 °C. Differences in the surface temperature (Ts) between each neighbourhood and the airport and city centre (derived from satellite images) were used to scale this 1.2 °C to UHI effect values for each neighbourhood.[18] Hourly air temperatures measured at Rotterdam Airport (Ta_airport) were corrected with this value to calculate hourly air temperatures for each neighbourhood (Ta_neighb). From this we could retrieve neighbourhood-specific daily maximum air temperatures (Ta_{max}) during the study period.

Neighbourhood-specific daily Tmrt and UTCI were both calculated using the SOLWEIG 1D (Solar and Longwave Environmental Irradiance Geometry) model.[15,19] Technical details of the exposure assessment using this model are descibred in the online supplement.

2.3. Air pollution exposure assessment

Daily exposure to particulate matter with a diameter of ≤10 µm (PM_{10}), nitrogen dioxide (NO_2) and ozone (O_3) were estimated for the study period, using dispersion modelling in combination with air quality measurements.[20] Because home addresses were not available, we determined daily population weighted average (PWA) concentrations per neighbourhood instead. These were calculated from the daily average concentrations for three different 'exposure situations' in each neighbourhood and calibrated with daily measurement data. These 'exposure situations' were: streets with more than 10,000 vehicles per day (Zone 1), areas up to 100 m from urban motorways (Zone 2) and the rest of the urban area in a neighbourhood (Zone 3). Subsequently, the PWA concentration for a given neighbourhood was computed taking into account the number of people (#) living in each of these zones:

$$\text{PWA } (\mu g/m^3) = ((C*\#)\text{Zone 1}+(C*\#)\text{Zone 2}+(C*\#)\text{Zone 3}) \,/\, (\#\text{Zone 1}+\#\text{Zone 2}+\#\text{Zone 3}) \quad (1)$$

with C the daily average concentration of a pollutant in µg/m^3 in each zone per neighbourhood.

Concentrations of PM_{10}, NO_2 and O_3 for Zone 3 in a neighbourhood were derived from background concentrations at 1*1 km spatial resolution grids. These background concentrations are based on a combination of modelling and measurements in the National Air Quality Monitoring Network.[21] The contribution of road traffic emissions from streets and motorways is added to the urban background in each neighbourhood (Zone 3 concentration) to obtain Zone 1 and 2 concentrations. More details on modelling of the traffic contributions are described in the online supplement.
The uncertainty involved in modelling the annual averages of regulated air pollutants at a certain location in the Netherlands has been estimated as 20%.[22] In this study, the modelled daily averages were calibrated by daily measurements and therefore a similar uncertainty is assumed for PM_{10}, NO_2 and O_3.

2.4. Study design and data analysis

The case-crossover design was used to assess the relations between heat, air pollution and mortality. This design is a modification of the matched case-control design in which each case acts as his/her own control, and distribution of exposure is compared between cases and controls. Exposure at the time of event (i.e. case date) is compared with a set of referent (control) dates that represent the expected distribution of exposure for non-event follow-up times.[22-24] This means that the individual mortality cases in our dataset were merged with heat and air pollution exposure in their neighbourhood of residence on the date of death as well as on three referent dates. The case date of a person was defined as the date of death. The three referent dates were selected by the time stratified method,[24-26] which implies that they are matched on day of the week, month and year with the case date of each subject. For example, when a case died on Monday the 6th of May 1996, referent dates were chosen on the 13th, 20th and 27th of May 1996, when a case died on Tuesday the 10th of June 1997, referent days were chosen on the 3rd, 17th and 24th of June 1997 and so on. This method of referent date selection explicitly controls for time trends, seasonality and chronic and slowly varying potential confounders.[24,27] Besides same-day exposures (lag 0), lag times of 1 and 2 days before the date of death, with referent dates chosen accordingly, were also evaluated.

Conditional logistic regression analyses were conducted to calculate odds ratios and corresponding 95% confidence intervals (CIs) associated with thermal exposure. Confounding and effect modification by air pollution were assessed using multivariate models.

It is known that the temperature-mortality association typically follows a U-, V-, or J-shaped curve, with increased mortality below and above a certain threshold, which varies by country or region.[8,28,29] In general, cold effects are delayed and last for many days, while heat effects appear quickly and do not last long.[4,5,30] Confounding or effect modification of cold and heat stress effects on mortality by air pollution may therefore be different, and is probably most efficiently studied by separate models. In this study, we chose to focus on the combination of heat stress and air pollution effects on natural-cause mortality.

One of the options to do this is to split the data in a cold and a warm season (e.g. October-March and April-September). However, the warm season data could have been "contaminated" with days below the threshold value causing attenuation of the heat stress effect, while days above the threshold value in the cold season data are lost. Therefore, we used all-year data with a quadratic (U-shape) term to model heat exposure. The quadratic term was centered at the average value of the specific heat exposure parameter, functioning as a reference for the increase in risk with increasing heat exposure. We only interpreted the heat-mortality relationship at the right "warm" end of the quadratic term. The air pollution parameters were included in the models as linear terms.

To focus the research, we first analysed univariate associations between all heat and air pollution exposure parameters and mortality. Subsequently, we selected the heat indicator and lag model with the lowest Akaike Information Criterion (AIC), and used the least correlated air pollution parameter to define multivariate and interaction models. Effect modification by air pollution was studied by including an interaction term effective from the threshold value (of the heat parameter) upwards (modelled as a spline with a knot at the threshold value) in the model. Multivariate and interaction models were built only for the selected parameters and lag time to avoid multiple testing, these were Ta_{max} and $PM_{10.}$ We chose PM_{10} over O_3 as pollution indicator, because O_3 was substantially correlated with temperature (Table 2). The multivariate models containing interaction terms between Ta_{max} and PM_{10} revealed significant effect modification of the temperature-mortality relationship by air pollution. Therefore, mortality risks are shown at different combinations of temperature and air pollution levels.

The following formulas describe the calculation of the mortality risks (MR) based on the estimates derived from the different univariate and multivariate conditional regression analyses:

- MR = EXP(B1*Ta_{max} centered + B2*(Ta_{max} centered^2))
- MR = EXP(B1*PM_{10}_IQR)
- MR = EXP(B1*Ta_{max} centered + B2*(Ta_{max} centered^2) + B3*PM_{10}_value + B4*(PM_{10}_value*Ta_{max} centered$^{\#}$)Where:

Ta_{max} centered = Ta_{max} – 14.27 (the average Ta_{max} value).

PM_{10}_value = the level of PM_{10} for which the mortality risk is calculated.

Ta_{max} centered$^{\#}$ = is 0 when Tamax is below 15 °C.

To investigate the extent of neighbourhood differences in heat-mortality risks, we looked at average differences in heat (Ta_{max}) and air pollution (PM_{10}) between neighbourhoods during warm days with high pollution (summer smog days), and translated these differences into differences in mortality risk increase.

Susceptible subgroups were identified by stratified analyses based on sex, age (<45, 45-64, 65-84 and ≥85 years), marital status (never married, married, widowed and divorced), ethnicity (Dutch, Western and non-Western origin) and household income quartiles (<14842 €/year, 14842-19850 €/year, 19850-26497 €/year, >26497 €/year). We compared the risk of mortality following "summer smog" days (Ta_{max} 25 ºC and PM_{10} 50 µg/m^3) (lag 2) between the different subgroups in the total population and in the population aged 65 or older.

3. Results

3.1. Study population

The average number of inhabitants in Rotterdam over the period 1995-2009 was ± 600.000 with approximately 5500 to 6000 deaths a year. For this study period, we were able to merge both meteorological and air pollution data to 73,178 mortality cases. Demographic characteristics of these cases and the cases aged ≥65 years are shown in Table 1. Household income data were available from 2003 onwards, for 26,381 cases. In the population aged 65 years or older, there was a larger proportion of people from Dutch origin, and widowed people than in the population as a whole.

3.2. Heat and air pollution exposure

Figure 1 shows the distribution of the various thermal and air pollution exposure indicators during the study period. Table 2 contains correlations between the different exposure parameters. Correlations between the different thermal indicators were substantial (i.e. between 0.75 and 0.95). The correlations between the different air pollution parameters were moderate (i.e. all smaller than 0.5). Finally, correlations between thermal and air pollution parameters were weak (i.e. between -0.22 and -0.02), except for ozone (with Pearson correlation coefficients ranging from 0.63-0.70).

3.3. Univariate associations between heat, air pollution and natural-cause mortality

Table 3 shows the univariate associations between the different heat parameters and mortality at lag 0, 1 and 2 days, while Table 4 shows the univariate associations between air pollution and mortality. The associations are expressed as percentage increase in risk (%)

and 95% confidence intervals for the increase between 90% and 99% of the specific thermal index (Table 3), and per iqr increase for the air pollution parameters (Table 4).

According to the AIC, Ta_{max} was the best performing thermal indicator at all lag times. Figure 2 shows the quadratic curves at different lags for the risk increase with Ta_{max} increasing or decreasing from the average exposure (14.27 ºC).

Table 4 shows that according to the AIC, PM_{10} was the best performing air pollution indicator at lag 0 and 2, while O_3 was the best performing indicator at lag 1.

3.4. Interaction between heat and air pollution

Figure 3, Figure 4, and Figure 5 show the interaction models at lag 0, 1 and 2 days. The AIC revealed that lag 2 was the best performing model.

Table 5 shows the frequency of certain temperature and air quality combinations (when Ta_{max} ≥ 15ºC) averaged over the total study area. On 2,679 days (48.9% of the total study period) Ta_{max} was 15 ºC or higher. The most frequent combination (27.3% of the days with Ta_{max} ≥ 15ºC) was a Ta_{max} between 15 and 20 ºC and a PM_{10} level between 15 and 30 μg/m^3 (further referred to as "reference" days). The increased risk of natural-cause mortality following these "reference" days lies between 0 and 3% (Figure 5). During 158 days (5.9% of the days with Ta_{max} ≥ 15ºC) the average Ta_{max} in the area was 25 ºC or higher combined with an average PM_{10} level exceeding the 24 hour limit value of 50 μg/m^3 (further referred to as "summer smog" days). The risk of natural-cause mortality was at least 7% higher after these "summer smog" days (lag 2) compared to the mortality risk following "reference" days (Figure 5).

3.5. Neighbourhood differences in heat-mortality risk

During "summer smog" days the maximum difference in Ta_{max} between neighbourhoods was 1.5 °C, while the difference in PM_{10} could reach almost 18.5 μg/m^3**.** The neighbourhood median Ta_{max} and PM_{10} levels during "summer smog" days are shown in Figure 6. When we compared mortality risks between neighbourhoods at the lowest and highest median "summer smog" level (i.e. Ta_{max} 27 °C & PM_{10} 62 μg/m^3 versus Ta_{max} 28.5 °C & PM_{10} 66 μg/m^3; lag 2) there was a mortality risk difference of almost 3%. This difference increased up to 7% after days with higher than median "summer smog" levels.

3.6. Vulnerable groups

The results are shown in Table 6, and reveal that mortality risk after "summer smog" days is higher in very elderly people (age 85+) compared to the mortality risk in the population as a whole. In the age group 65+ people who are never married or widowed seemed more susceptible, while people from non-Dutch origin seemed less susceptible. Income data were only available from 2003-2009. Hence, results of this sub-analysis might not be completely comparable to the whole sample. Yet, the results point to a decreased risk in the highest income group.

4. Discussion

4.1. Main findings

In this study, maximum daily air temperature was the best thermal indicator to investigate heat-related mortality. We found significant effect modification of the heat-mortality relationship by air pollution (PM_{10}). Stratified analyses showed that single living elderly were more susceptible to heat stress than people who are younger and/or married. Mortality risks varied substantially between neighbourhoods, on "summer smog" days the difference was on average 3%, but could increase up to a difference of 7%.

The association between heat and natural-cause mortality is in line with earlier studies in the Netherlands.[6,31] Huynen et al.[31] studied the impact of ambient temperature, particularly the impact of heat waves and cold spells, on mortality over the period 1979-1997 in the Netherlands. They found a V-like relationship between temperature and mortality, with an increase in heat-related mortality of 2.72% for each degree Celsius increase above 16.5 ºC. Average total excess mortality during the heat waves in the study period was 12.1%. However, temperature data were derived from a single site, and the mortality effects were not controlled for air pollution. Another study in the Netherlands comprised the excess deaths that occurred during the hot summer (including a heat wave and smog period) of 2003. Based on a quick screening the authors concluded that: "a significant proportion of the deaths now being attributed to the hot summer weather can reasonably be expected to have been caused by ambient ozone and, to some extent, particles."[6] However, they did not specify the exact proportions caused by high temperatures, by air pollution, and their interaction.

Earlier studies elsewhere also often used temperature and air quality data measured at a single site,[3] and assumed that exposure across cities is the same. This causes misclassification of exposure, and probably an underestimation of temperatures in inner-city areas. Non-differential misclassification could be more pronounced among vulnerable groups who spend more time indoors or live in areas with less thermal comfort. Effect estimates could then be biased towards the null.[3] Exposure assessment on neighbourhood level reduces the amount of misclassification. This allowed us to demonstrate that synergistic effects of heat and air pollution even occur in cities with a temperate climate and relatively low air pollution.

4.2. Limitations of the exposure assessment

Exposure assessment at the exact addresses of the cases in our study population would have been more accurate, but was not possible due to privacy regulations. Besides this limitation, there was a lack of data on behavioural and physical factors like the use of air conditioning, time spent outdoors or away from home, and the orientation, insulation and ventilation of the home that could have influenced the impact of outdoor temperature on personal exposure.

Another limitation was that a constant value of 1.2 °C was used to estimate the annual mean UHI-effect for each neighborhood. Hourly air temperatures measured at Rotterdam Airport were corrected with this annual mean UHI-effect to calculate hourly air temperatures for each neighbourhood. In reality, the UHI effect varies over time, differs between seasons, differs between day and night and also depends on the meteorological situation: air temperature, wind speed, atmospheric stability, cloud coverage. Ideally, we would have taken this into account and calculated a daily UHI-effect for each neighborhood. However, no simple parameterization yet exists that takes into account all these effects to derive a daily or hourly in-city temperature from an out-city temperature. The UHI-effect is generally largest during warm days because of more solar radiation, but can also be large during winter days because of the enhanced anthropogenic heat during winter times. The UHI-effect generally decreases for higher wind speeds, for higher cloud coverage and for stable atmospheric situations. All these effects could not be included straightforwardly.

4.3. The use of different thermal indicators

By using various thermal indicators we could investigate the importance of other meteorological factors in addition to temperature. Other studies have also compared different thermal indices in relation to mortality, but on a less detailed level. Morabito et al.[32] showed that direct multivariate indices including the effect of wind speed, solar radiation, air humidity and temperature fitted best with all-cause very elderly mortality attributable to heat stress. In that study, the UTCI performed best in thermal comfort assessment, but was not the best predictor of mortality. A study in the Czech Republic found similar heat effects on CVD mortality for air temperature and the examined thermal indices (UTCI, AT and Physiologically Equivalent Temperature (PET)).[33] These studies show that there is no strong evidence to favour the use of a specific thermal indicator over the use of air temperature alone when studying heat-related mortality. Different thermal indicators may have different impact on mortality depending on geographical context. Therefore, it seems worthwhile to consider a few of them when designing heat-mortality studies. To avoid multiple testing and collinearity problems, we only used Ta_{max} and PM_{10} in the multivariate and interaction models.

4.4. Susceptibility to heat-related mortality

As has been found in earlier studies, stratified analysis of the temperature mortality association showed that the very elderly (age 85+) were more vulnerable to the effects of heat and air pollution than people from younger age groups. This may be caused by a weakened thermal regulatory system.[10] However, age was also associated with other potentially important determinants, such as sex, ethnicity, marital status, and household income. For example, the proportions of women, and of widowed people are larger in the older age groups. Therefore, we also performed stratified analyses in people age 65 and older. This showed slightly different results from the stratified analyses in the total population. Besides the very elderly it seemed that people who are widowed or divorced or with a low household income are also more vulnerable. These people may receive less social attention and may have less resources to take preventive measures to cope with heat stress.[1] These groups have also been mentioned by Stafoggia et al.[10] in Italy and Tian et al.[34] in China. In addition, both studies mentioned people with pre-existing medical condition (psychiatric disorders, depression, heart conduction disorders, circulatory disorders of the

brain), and people who reside in nursing homes or hospitals.[10,34] There was no information on those factors in our study. People from non-Dutch origin seemed less vulnerable than people from Dutch origin. This may be explained by the fact that they largely come from Turkey, Morocco and Surinam, countries with a much warmer climate than the Netherlands. These people may be more capable to acclimatize and/or adapt to higher temperatures.
A limitation in our study was the incomplete household income data (only available after 2003). Hence, results regarding household income may not be completely comparable with results regarding the other susceptibility variables.

4.5. Case-crossover versus time-series studies

The advantage of the case-crossover over a time series design is that each subject serves as his or her own control. Hence, the influence of confounders that remain constant in the subject such as sex and smoking history is controlled for by design. Time-stratified selection of referent dates on the same day of the week in the same month as the case date provides adequate control for long-term trends, seasonality, day of the week and month. Potential interaction between exposures can be assessed at individual rather than at the group level.[23,24] In addition, an issue in time-series studies is that the composition and size of the total population at risk may vary because of the effects of prior exposures, which might happen when after the first warm days very frail individuals are affected earlier than others ("harvesting effect"). In that case, positive associations found over the first warm days might be offset by negative associations over the subsequent warm days.[3] This problem is avoided when using a case-crossover design, because exposure and event are assessed at the individual level rather than at the population level.[25]

5. Conclusions

We found significant synergistic effects of high temperatures and air pollution on natural-cause mortality in a city with a temperate climate. Single living elderly are the most vulnerable group. Due to the urban heat island effect and spatial differences in air pollution levels, mortality risks vary substantially between neighbourhoods, with a difference up to 7%.

Acknowledgements

This study was conducted as part of the URGENCHE project funded by European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no 265114.

6. References

1. Basu R, Samet J. Relation between elevated ambient temperature and mortality: a review of the epidemiologic evidence. Epidemiol Rev 2002;24:190-202.

2. Basu R, Feng WY, Ostro BD. Characterizing temperature and mortality in nine California counties. Epidemiology 2008; 19: 138-145.

3. Basu R. High ambient temperature and mortality: a review of epidemiologic studies from 2001 to 2008. Environ Health 2009; 8: 40.

4. Yu W, Mengersen K, Wang X, Ye X, Guo Y, Pan X, Tong S. Daily average temperature and mortality among the elderly: a meta-analysis and systematic review of epidemiological evidence. Int J Biometeorol 2012; 56: 569-581.

5. Guo Y, Gasparrini A, Armstrong B, Li S, Tawatsupa B, Tobias A, et al. Global variation in the effects of ambient temperature on mortality: a systematic effect. Epidemiology 2014; 25: 781-789.

6. Fischer PH, Brunekreef B, Lebret E. Air pollution related death during the 2003 heat wave in the Netherlands. Atmos Environ 2004; 38: 1083-1085.

7. Stafoggia M, Schwartz J, Forastiere F, Perucci CA and the SISTI group. Does temperature modify the association between air pollution and mortality? A multicity case-crossover analysis in Italy. Am J Epidemiol 2008; 167: 1467-1485.

8. Keatinge WR, Donaldson GC, Cordioli E, Martinelli M, Kunst AE, Mackenbach JP, et al. Heat related mortality in warm and cold regions of Europe: observational study. BMJ 2000; 321: 670-673.

9. Schwartz J. Who is sensitive to extrems of temperature? Epidemiology 2005; 16:67-72.

10. Stafoggia M, Forastiere F, Agostini D, Biggeri A, Bisanti L, Cadum E, et al. Vulnerability to heat related-mortality. A multicity, population-based, case-crossover analysis. Epidemiology 2006; 17: 315-323.

11. Oke TR. Boundary layer climates. 2nd ed. London: Methuen; 1987.

12. Voogt JA. Urban heat islands: hotter cities. November 2004. Available at: http://www.actionbioscience.org/environment/voogt.html?print

13. CBS Statistics Netherlands. Definitions Standardised income. http://www.cbs.nl/en-GB/menu/methoden/begrippen/default.htm?Languageswitch=on&ConceptID=291. Accessed November 21, 2014.

14. Dutch Code of Conduct for Medical Research. http://www.federa.org/code-goed-gedrag. Accessed November 21, 2014.

15. Lindberg F, Grimmond CSB. The influence of vegetation and building morphology on shadow patterns and mean radiant temperature in urban areas: model development and evaluation. Theor Appl Climatol. 2011; 105: 311-323.

16. Thorsson S, Rocklov J, Konarska J, Lindberg F, Holmer B, Dousset B, et al. Mean radiant temperature – a predictor of heat related mortality. Urban Climate. 2014; DOI: 10.1016/j.uclim.2014.01.004.

17. Jendritzky G, de Dear R, Havenith G. UTCI – Why another thermal index? Int J Biometeorol. 2012; 56: 421-428.

18. Klok L, Zwart S, Verhagen H, Mauri E. The surface heat island of Rotterdam and its relationship with urban surface characteristics. Resour Conserv Recy. 2012; 64: 23-29.

18. Lindberg F. The SOLWEIG-model. Gothenburg University, Sweden. 2013.

20. Keuken MP, Zandveld P, van den Elshout S, et al. Air quality and health impact of PM_{10} and EC in the period 1985-2008 in the city of Rotterdam, the Netherlands. *Atmos Environ*. 2011; 45: 5294-5301.

21. Velders GJM, Aben JMM, Geilenkirchen GP, et al. Large scale air quality and deposition maps for the Netherlands, 2013 (in Dutch). RIVM, Bilthoven, the Netherlands. Available at: www.rivm.nl/Documenten_en_publicaties/Wetenschappelijk/Rapporten/2013/mei/Grootschalige_concentratie_en_depositiekaarten_Nederland_Rapportage_2013.

22. Mathijssen J, Visser H. PM_{10} in the Netherlands: modelling, concentrations and uncertainties (in Dutch). RIVM, Bilthoven, the Netherlands. 2006. Available at: www.rivm.nl/bibliotheek/rapporten/500093005.pdf.

23. Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. Am J Epidemiol 1991; 133: 144-153.

24. Basu R, Dominici F, Samet J. Temperature and mortality among the elderly in the United States. A comparison of epidemiologic methods. Epidemiology. 2005; l16: 58-66.

25. Carracedo-Martínez E, Taracido M, Tobias A, Saez M, Figueiras A. Case-crossover analysis of air pollution health effects: a systematic review of methodology and application. Environ Health Perspect. 2010; 118: 1173-1182.

26. Lumley T, Levy D. Bias in the case-crossover design: implications for studies of air pollution. Environmetrics. 2000; 11: 689-704.

27. Levy D, Lumley T, Sheppard L, et al. Referent selection in case-crossover analyses of acute health effects of air pollution. *Epidemiology*. 2001; 12: 186-192.

28. Guo Y, Barnett AG, Pan X, Yu W, Tong S. The impact of temperature on mortality in Tianjin, China: A case-crossover design with a distributed lag non-linear model. Environ Health Persp. 2011; 119: 1719-1725.

29. Zhang J, Li TT, Tan JG, Huang CR, Kan HD. Impact of temperature on mortality in three major Chinese cities. Biomed Environ Sci 2014; 27: 485-494.

30. Wichmann J, Jovanovic Andersen Z, Ketzel M, Ellermann T, Loft S. Apparent temperature and cause-specific mortality in Copenhagen, Denmark: a case-crossover analysis. Int J Environ Res Public Health. 2011; 8: 3712-3727.

31. Huynen MMTE, Martens P, Schram D, Weijenberg M, Kunst A. The impact of heat waves and cold spells on mortality rates in the Dutch population. Environ Health Persp. 2001; 109: 463-470.

32. Morabito M, Crisci A, Messeri A, Capecchi V, Modesti PA, Gensini GF, et al. Environmental temperature and thermal indices: What is the most effective predictor of heat-related mortality in different geographical contexts? The Scientific World Journal 2014; Article ID 961750.

33. Urban A, Kyselý J. Comparison of UTCI with other thermal indices in the assessment of heat and cold effects on cardiovascular mortality in the Czech Republic. Int J Environ Res Pub Health 2014; 11: 952-967.

34. Tian Z, Li S, Zhang J, Jaakkola JJK, Guo Y. Ambient temperature and coronary heart disease mortality in Beijing, China: a time series study. Environ Health 2012; 11: 56.

7. Tables

Table 1. Demographic characteristics of the study population

Case characteristics	Total	Age ≥ 65 years
Natural-cause mortality cases (absolute n over 1995-2009)	73,178	60,407
Age category (n, (%))		
<45 years	2,679 (3.7)	-
45-64 years	10,092 (13.8)	-
65-84 years	36,339 (49.7)	36,339 (60.2)
≥85 years	24,068 (32.9)	24,068 (39.8)
Sex (n, (%))		
Male	33,816 (46.2)	26,088 (43.2)
Female	39,362 (53.8)	34,319 (56.8)
Ethnicity (n, (%))		
Dutch origin	62,766 (85.8)	54,349 (90.0)
Western origin	5,168 (7.1)	3,880 (6.4)
Non-western origin	5,208 (7.1)	2,177 (3.6)
Marital status (n, (%))		
Never married	8,461 (11.6)	4,976 (8.2)
Married	25,936 (35.4)	20,377 (33.7)
Widowed	29,866 (40.8)	29,258 (48.4)
Divorced	8,915 (12.2)	5,796 (9.6)
Household income[a] (n, (%))		
cat1 (<14842 €/year)	13,853 (52.5)	11,856 (54.1)
cat2 (14842-19850 €/year)	7,014 (26.6)	5,980 (27.3)
cat3 (19850-26497 €/year)	3,311 (12.6)	2,497 (11.4)
cat4 (>26497 €/year)	2,203 (8.4)	1,599 (7.3)

a. Standardised household income, corrected for differences in size and composition of the household.

Table 2. Correlation between the various thermal and air pollution indices during the study period

	Ta_{max}	$Tmrt_{max}$	$UTCI_{max}$	PM_{10}	NO_2	O_3
Ta_{max}	1.00					
$Tmrt_{max}$	0.78	1.00				
$UTCI_{max}$	0.91	0.92	1.00			
PM_{10}	-0.02	-0.02	0.02	1.00		
NO_2	-0.26	-0.22	-0.17	0.48	1.00	
O_3	0.63	0.70	0.64	-0.12	-0.40	1.00

Ta_{max}: daily maximum air temperature, $Tmrt_{max}$: daily maximum mean radiant temperature, $UTCI_{max}$: daily maximum Universal Thermal Comfort Index, PM_{10}: particulate matter with diameter of 10 micrometers or less, NO_2: nitrogendioxide, O_3: ozone

Table 3. Percentage risk increase of natural-cause mortality for an increase between the 90 and 99% of the thermal index at different lag times, derived from univariate conditional logistic regression models

Parameter	Lag	90-99%	% risk increase	p-value	AIC
Ta_{max}	0	23.3-30.1	9.3	<0.01	215953
$Tmrt_{max}$	0	55.8-61.9	2.6	<0.01	215974
$UTCI_{max}$	0	31.6-37.6	6.4	<0.01	215960
Ta_{max}	1	23.3-30.1	10.6	<0.01	215899
$Tmrt_{max}$	1	55.8-61.9	4.0	<0.01	215903
$UTCI_{max}$	1	31.6-37.6	7.5	<0.01	215901
Ta_{max}	2	23.3-30.1	9.2	<0.01	215806
$Tmrt_{max}$	2	55.8-61.9	2.7	<0.01	215819
$UTCI_{max}$	2	31.6-37.6	6.2	<0.01	215808

Table 4. Percentage risk increase of natural-cause mortality per iqr increase in air pollution parameter at different lag times, derived from univariate conditional logistic regression models

Parameter	Lag	Median (IQR)	% risk increase	95% CI	AIC
PM_{10}	0	31.8 (20.8)	1.7	(0.8-2.6)	215973
NO_2	0	38.3 (19.9)	1.1	(-0.3-2.4)	215983
O_3	0	42.0 (34.6)	2.9	(1.1-4.7)	215974
PM_{10}	1	31.8 (20.8)	1.6	(0.6-2.5)	215925
NO_2	1	38.3 (19.9)	0.5	(-0.4-1.4)	215927
O_3	1	42.0 (34.6)	3.4	(1.6-5.3)	215923
PM_{10}	2	31.8 (20.8)	1.2	(0.2-2.1)	215827
NO_2	2	38.3 (19.9)	1.7	(0.4-3.1)	215827
O_3	2	42.0 (34.6)	1.4	(-0.4-3.2)	215831

Table 5. Number of days with a certain temperature and air quality combination during study period (when $Ta_{max} \geq 15ºC$) (n (%))

Ta_{max}	PM_{10}					
	<15 $\mu g/m^3$	15-30 $\mu g/m^3$	30-50 $\mu g/m^3$	50-70 $\mu g/m^3$	>70 $\mu g/m^3$	Total
15 – 19 ºC	30 (1.1)	730 (27.3)	423 (15.8)	111 (4.1)	51 (1.9)	1345 (50.2)
20 – 24 ºC	6 (0.2)	377 (14.1)	400 (14.9)	140 (5.2)	38 (1.4)	961 (35.9)
25 – 29 ºC	0 (0.0)	53 (2.0)	135 (5.0)	79 (3.0)	46 (1.7)	313 (11.7)
30 – 36 ºC	0 (0.0)	6 (0.2)	21 (0.8)	14 (0.5)	19 (0.7)	60 (2.2)
Total	36 (1.3)	1166 (43.5)	979 (36.5)	344 (12.8)	154 (5.8)	2679 (100.0)

Table 6. Percentage risk increase of natural-cause mortality on "summer smog" days (Ta_{max} 25 ºC; PM_{10} 50 μg/m^3) (lag 2) stratified for potentially vulnerable groups in the total population and in the population aged 65 or older

Substrata	**Total population**	**Population aged 65+**
	% risk increase 95% CI	% risk increase 95% CI
Age category (n, (%))		
<45 years	7 (6-9)	-
45-64 years	8 (7-9)	-
65-84 years	6 (5-6)	-
≥85 years	10 (9-11)	-
Sex (n, (%))		
Male	8 (7-8)	8 (7-8)
Female	7 (7-7)	7 (7-8)
Ethnicity (n, (%))		
Dutch origin	8 (7-8)	8 (7-8)
Western (non-Dutch) origin	5 (4-7)	6 (4-8)
Non-western origin	8 (7-10)	4 (2-6)
Marital status (n, (%))		
Never married	9 (8-10)	9 (7-10)
Married	7 (6-7)	5 (4-6)
Widowed	10 (9-10)	9 (9-10)
Divorced	1 (0-2)	3 (2-4)
Household income (n, (%))		
cat1 (<14842 €/year)	12 (10-13)	15 (14-17)
cat2 (14842-19850 €/year)	14 (11-15)	11 (9-13)
cat3 (19850-26497 €/year)	17 (14-20)	20 (16-24)
cat4 (>26497 €/year)	1 (-3-5)	-3 (-7-1)

8. Figures

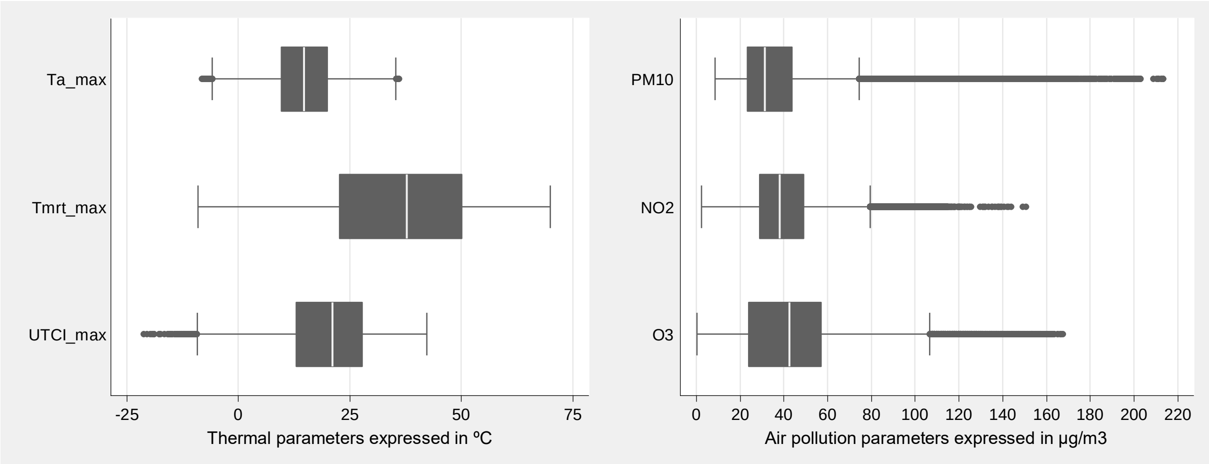

Figure 1. Distribution of thermal and air pollution exposure during the study period

Ta_{max}: daily maximum air temperature, $Tmrt_{max}$: daily maximum mean radiant temperature, $UTCI_{max}$: daily maximum Universal Thermal Comfort Index, PM_{10}: particulate matter with diameter of 10 micrometers or less, NO_2: nitrogendioxide, O_3: ozone

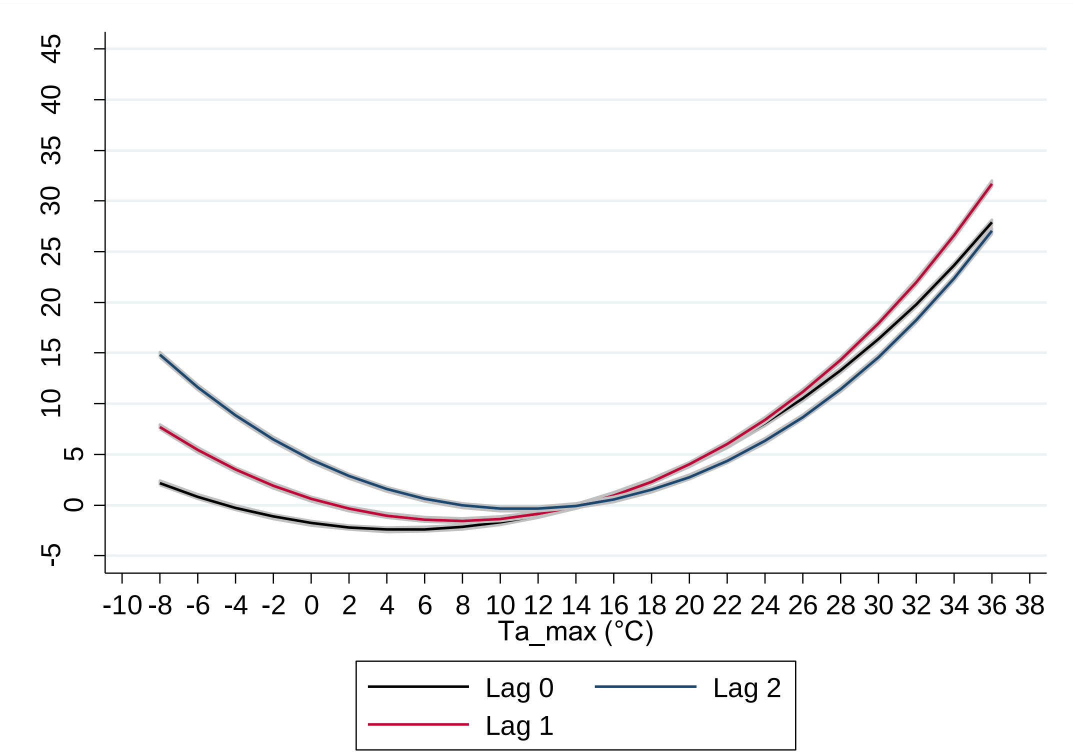

Figure 2. Univariate association between Ta_{max} and natural-cause mortality at different lag times.

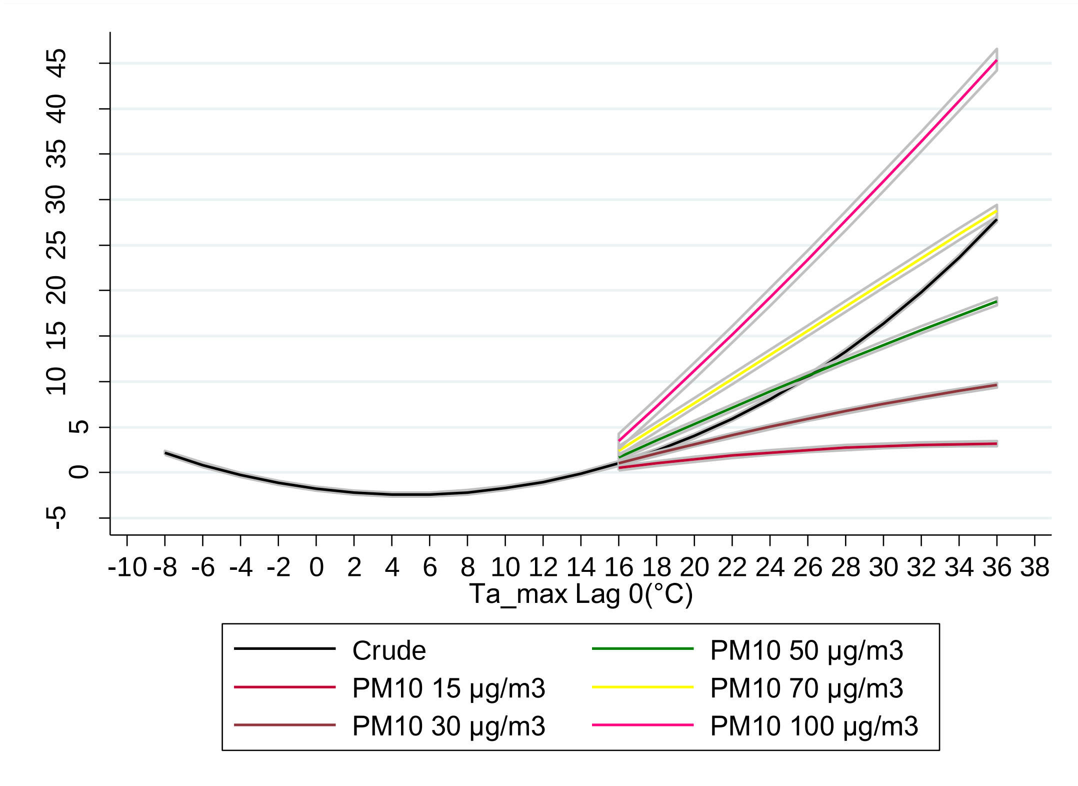

Figure 3. Interaction between Ta_{max} and PM_{10} of the effect on natural-cause mortality at lag 0 (AIC 215942).

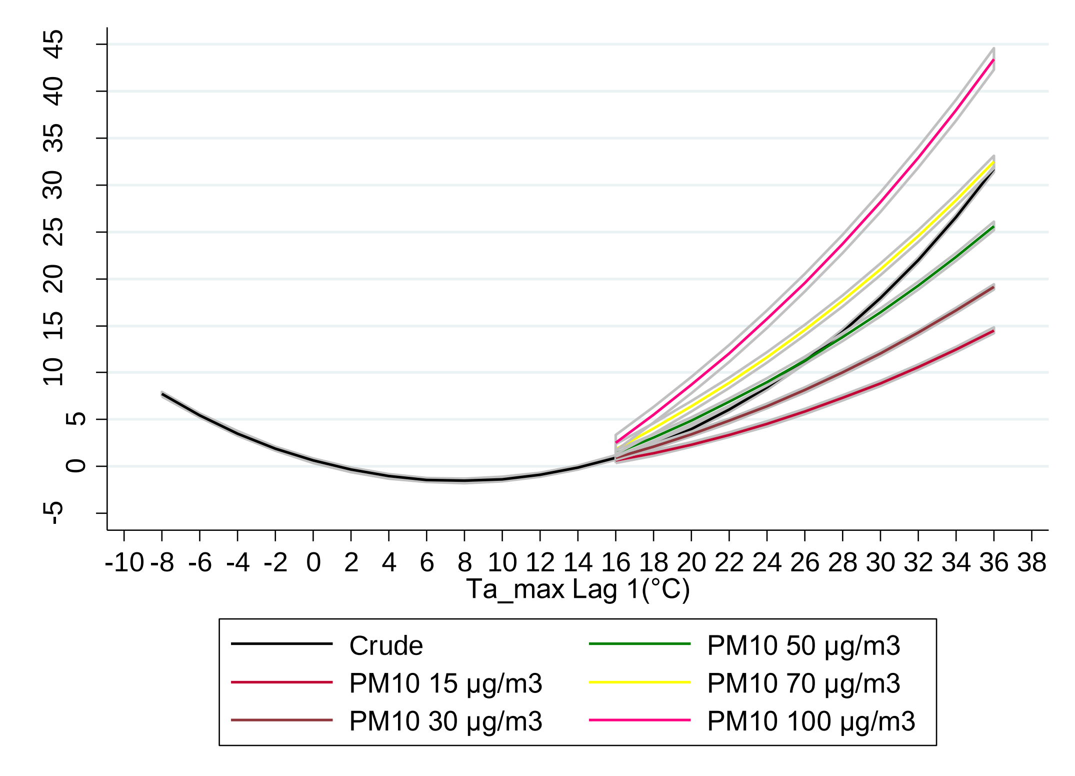

Figure 4. Interaction between Ta_{max} and PM_{10} of the effect on natural-cause mortality at lag 1 (AIC 215896).

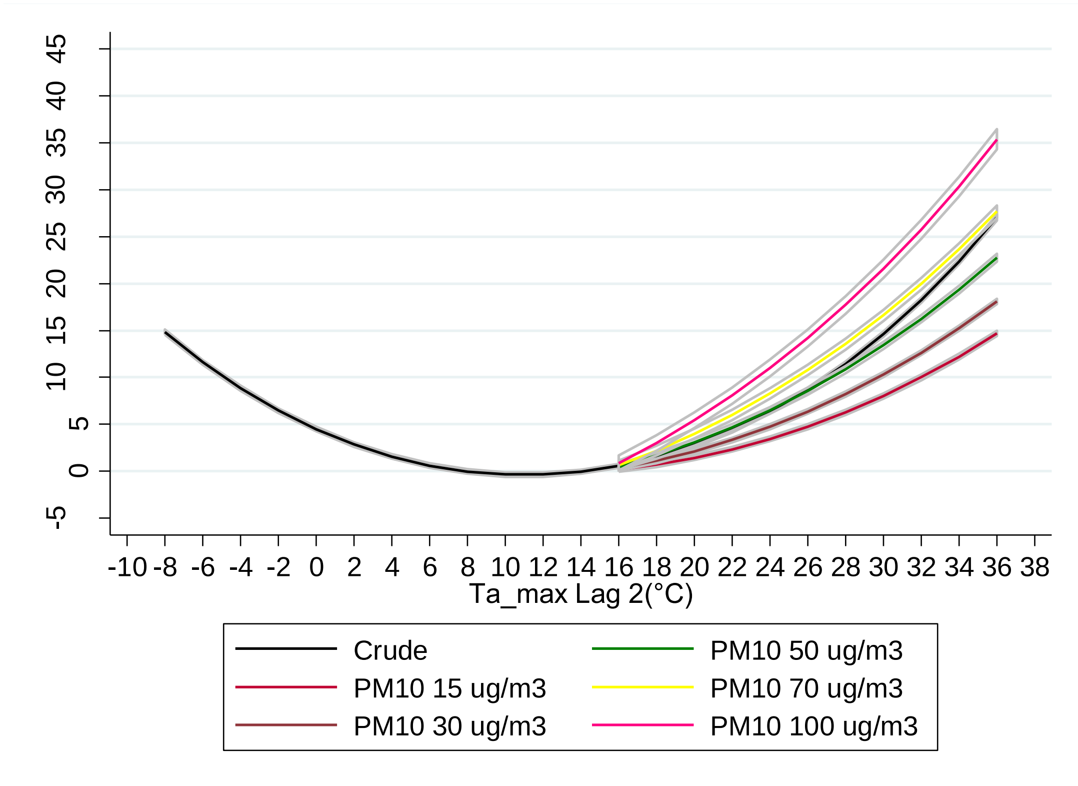

Figure 5. Interaction between Ta_{max} and PM_{10} of the effect on natural-cause mortality at lag 2 (AIC 215806).

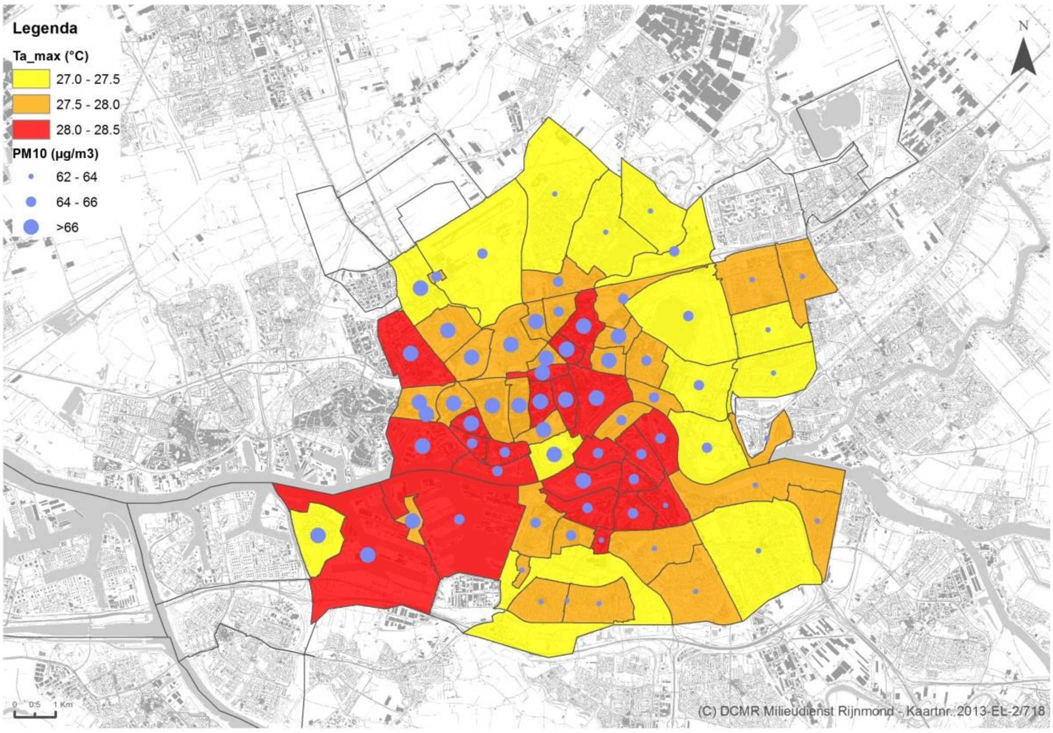

Figure 6. Median Ta_{max} and PM_{10} levels during "summer smog" d